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Acute Myeloid Leukemia as a Second Malignancy: Report of 9 Pediatric Patients in a Single Institution in Argentina

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Background. Acute myeloid leukemia (AML) is well-recognized as one of the most important second malignancies. We report the occurrence of secondary AML (sAML) in our institution.

Procedure. From September 1987 to August 1996 we have observed sAML in 9 patients (median age 4 years), 5 of them previously treated for hematologic malignancies (group I): acute lymphoblastic leukemia (n = 2), AML (n = 1), non-Hodgkin lymphoma (n = 1), Hodgkin disease (n = 1), and 4 of these 9 patients treated for solid tumors (group II): neuroblastoma (n = 1), retinoblastoma (n = 1), Wilms tumor (n = 1), and central nervous system germinoma (n = 1).

Results. All the patients had topoisomerase II inhibitors as part of treatment of their first malignancy, but only 5 patients received epipodophyllotoxins. Alkylating agents were part of primary therapy in 8 of 9 patients. The latency period for the development sAML was 26.5 (range = 2–55) months. The morphologic FAB features of sAML were M5 (n = 5), M4 (n = 3), and M2 (n = 1). Cytogenetic studies showed r11q23 in 3 patients, all of them with prior hematological malignancies. Initial therapy for sAML in all cases was chemotherapy (including cytarabine in combination with idarubicin and etoposide or doxorubicin or mitoxantrone). Three patients died during induction and 6 achieved complete hematologic response. Three of these patients remain disease free at +15, +51, and +99 months post-remission (including one post allogeneic BMT). The remaining 3 patients died, 1 in complete remission one month after diagnosis and 2 relapsed and died with progressive disease (one post allogeneic BMT).

Conclusions. Secondary AML is a sequela of oncologic treatments with specific cytogenetic abnormalities and poor outcome. A few patients can achieve long-term survival even with standard chemotherapy. Med. Pediatr. Oncol. 30:160–164, 1998.

Key words: secondary acute myeloid leukemia; childhood cancer; leukemogens

INTRODUCTION

Intensive treatment with combination of cytotoxic drugs have improved cure rates in childhood malignancies over the two decades. Long-term effects after such therapies are a matter of increasing concern [1–3]. The incidence of second malignancies was estimated to be 8% to 12% from first diagnosis. Bone sarcomas were the most common second malignant neoplasms in children, developing in previously irradiated sites, while acute leukemia was the most common malignant disease not associated with radiation in the update from the Late Effects Study Group [4]. Most of these leukemias, named therapy-related leukemias or secondary leukemias, are acute myeloid leukemias (AML), although there are a few cases of acute lymphoblastic leukemias (ALL) [5]. Secondary AML (sAML) represents a separate entity in the spectrum of AML [6]. Until very recently alkylating agents were considered to be the principal cause of sAML [7]. However, other drugs that act as inhibitors of DNA topoisomerases, including epipodophyllotoxins, dactinomycin, anthracyclines, and dioxiperazine derivatives, have been included in the list of responsible factors in the production of sAML [8–10].

We report the characteristics and outcome of 9 patients with sAML treated in our institution in the last 9 years.

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MATERIALS AND METHODS

Patients

From September 1987 to August 1996, 3033 new consecutive children were admitted at the Hematology-Oncology department of the Hospital de Pediatría J.P. Garrahan with a diagnosis of malignant disease. All of these patients were younger than 20 years of age. We arbitrarily divided the patients, for this analysis, in two groups: Group I composed of children with primary hematological malignancies (ALL, AML, non-Hodgkin lymphoma and Hodgkin disease) (n = 1093) and group II constituted by patients with primary solid tumors (n = 1940). In group I, 770 were acute leukemias and 138 of them were AML. Of this group, 9 had secondary leukemias (6.5%). Informed consent was obtained from all patients and the investigations were approved by the institution's review committee for clinical trials.

Diagnostic Evaluation

The original pathologic tissue specimens from the first malignancies were reviewed in all nine cases. The diagnosis of AML as a second neoplasm was based on the presence of >30% abnormal blasts by morphology of bone marrow aspirate using May-Grunwald-Giemsa stain, peroxidase, Sudan Black, chloroacetate, alpha-naphthol acetate and butyrate esterase stains. Fluoride inhibition was used with alpha-naphtol acetate esterase stain to confirm the presence of monoblast-derived cells. The diagnosis was based on the morphology and cytochemical criteria of the French-American-British (FAB) Cooperative Working Group [11]. Standard immunophenotyping of leukemia blasts was performed as previously described [12].

Chromosome analysis of bone marrow specimens was performed directly or by a modified 24 hours culture method [13] in specimens obtained at original diagnosis and at the time of sAML. Eleven to 25 G-banded metaphases were analyzed in each case. Chromosome identification and karyotype designation were made according to the International System for Human Cytogenetic Nomenclature [14]. Molecular biology studies were not performed in these patients.

Treatment

The treatment history and the cumulative dosages of epipodophyllotoxins and alkylating agents used during primary treatment were reviewed for all nine patients. Salvage treatment for patients with sAML comprised a schedule similar to AML-BFM-87 Study and consisted of an 8-day induction phase with cytarabine as a 48-hour intravenous infusion (100 mg/m^2), followed by a 30-minute intravenous infusion (100 mg/m^2) every 12 hours for the next 6 days, idarubicin at dose of 12 mg/m^2 in 30-minute intravenous infusion on day 3–5, and etoposide (150 mg/m^2) in a 60-minute infusion on day 6–8. This induction phase, named ''AIE'', was followed by a 6-week consolidation phase with 8 drugs (prednisone, mercaptopurine, vincristine, doxorubicin, cytarabine, cyclophosphamide, and intrathecal cytarabine plus dexamethasone). After the consolidation phase, two courses of high dose cytarabine (3 g/m^2 every 12 hours × 6 doses) and etoposide (4 doses of 125 mg/m^2) were administered as intensification. Treatment was continued with a maintenance phase of daily thioguanine (40 mg/m^2/day) and monthly cytarabine (40 mg/m^2/day for 4 days) to completion 18 months from the diagnosis of AML [15]. Bone marrow transplantation was considered in patients with sAML when complete remission was achieved and a sibling HLA compatible donor was available.

RESULTS

The presenting clinical and biological features of 9 patients at initial diagnosis and at the time of developing sAML are summarized in Table I. Five were girls and 4 were boys, whose ages at the moment of their first diagnosis ranged from 9 months to 11 years old (median: 4 years). Of interest, one group of patients (Group I) was constituted by patients with a previous hematologic malignancy (n = 5) whereas group II was composed of patients with solid tumors (n = 4). In group I acute leukemia was the first diagnosis in 3 patients: two of them were ALL (common and pre-B ALL) and one was AML (FAB M4 with eosinophils). One patient had a stage III lymphoblastic non-Hodgkin lymphoma and 1 had a stage IIIB Hodgkin disease as the first malignancy. In group II the first diagnoses were: 1 patient with stage IV neuroblastoma with metastasis in a distant lymph node, 1 patient with stage I Wilms tumor, 1 patient with retinoblastoma, and 1 patient with central nervous system germinoma. All patients received adequate treatment as well as suitable pediatric support.

The drugs, cumulative dosages, and latency periods to development of sAML in our series are shown in Table I. All the patients had received a topoisomerase II inhibitor, but in only 5 of these treatments, epipodophyllotoxins were included (3 in group I and 2 in group II). Cumulative doses of epipodophyllotoxins were variable: teniposide was administered in 3 patients (750, 800 and 2100 mg/m^2) and etoposide in 3 patients (1350, 4000, and 4100 mg/m^2). Only 1 patient received these two drugs. Alkylating agents were part of the original schedule in 8 children: the mean cumulative doses of cyclophosphamide was 3,000 mg/m^2 in group I and 4,000 mg/m^2 in group II. The latency period to develop a secondary acute myeloid leukemia was variable: in group I the median time was 29 months and in group II 21 months, respectively. There was no significant differences between the two groups.

TABLE I. Clinical and Biological Characteristics of Patients Developing sAML

	First Malignancy					Second Malignancy		
Group	Age (years)	Sex	Tumor type	Treatment	Chemo. doses mg/m^2	Latency period (months)	FAB Sub type	Cytogenetic Findings
I-Prior Hematologic Malignancies								
1	1	F	ALL	Pred, VCR, DNR, Doxo, L-Asa, MP, Ara-C, CPM, MTX	CPM = 3000 DNR/Doxo = 240	55	M4	
2	11	F	HD	CPM,Pred, VCR, Procarb, Doxo, CCNU, VM-26 RT: 30.6 Gy Mantle& Inv. Y	CPM = 2400 VM-26 = 800 Doxo = 200	10	M5	47 XX / +8
3	9	F	ALL	Pred, VCR, DNR, Doxo, L-Asa, Ara-c, MP, CPM, MTX, VM-26, VP-16. RT: 24 Gy	CPM = 5800 DNR/Doxo = 280 VM-26 = 2100 VP-16 = 4100	45	M5	46 XX, t(9;11)(q21;q23)
4	5	M	NHL ''T''	Pred, VCR, DNR, Doxo, L-Asa, Ara-C, MP, CPM, MTX. RT: 24Gy	CPM = 2000 DNR/Doxo = 240	23	M5	46 XY t(9;11)(q21;q23)
5	4	F	AML (M4 Eo)	Ida, Doxo, Ara-C, VP-16, VCR, Pred, MP, TG, CPM	CPM = 1000 Ida/Doxo = 280 VP-16 = 1350	29	M2	46 XX t(1;11)(q36;q23)
II-Prior Solid Malignancies								
6	2	M	NBT	CDDP, VM-26, Doxo, CPM. RT: 31.5 Gy Tumor bed+ 20 Gy Metastatic node.	CPM = 5250 VM-26 =750 Doxo = 175	25	M4	
7	1	F	WT	DACT, VCR	DACT = 0.18	36	M4	46 XX/Del (6)(q?)
8	0.8	M	RTB	VCR, Doxo, CPM	CPM = 2100 Doxo = 120	2	M5	
9	5	M	CNS Germinoma	Ifo, VP-16, Carbo, VCR, CPM. RT: 25 Gy Craneospinal + 25 Gy local boost.	CPM = 16500 Ifo = 72000 VP-16 = 4000	32	M5	46 XY / 20q-

ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia, NHL: Non-Hodgkin lymphoma, HD: Hodgkin disease: NBT: neuroblastoma, WT: Wilms Tumor, RTB: Retinoblastoma, CNS: Central nervous system, Pred: prednisone, VCR: vincristine, DNR: daunorubicin, Doxo: doxorubicin, Ida: idarubicin, L-Asa: L-asparaginase, Ara-C: cytarabine, MP: mercaptopurine, TG: thioguanine, MTX: methotrexate, CPM: cyclophosphamide, VM-26: teniposide, VP-16: etoposide, CDDP: cisplatin, Procarb: procarbazine, DACT: dactinomycin and Ifo: ifosfamide, RT: radiotherapy.

All patients but one had completed their primary treatment and were in complete remission at the onset of sAML. In group II, patient #8 was on treatment for his retinoblastoma when sAML developed. His eye had been enucleated and at the moment of sAML onset, he was receiving the second course of chemotherapy. Also in group II, patient #9, with a germinoma in the central nervous system, had achieved a complete remission only with chemotherapy when he suffered a local relapse. A second complete remission was obtained with high dose cyclophosphamide and radiotherapy (25 Gy cerebrospinal and 50 Gy after as local boost).

In 8 out of 9 patients with sAML the bone marrow smears showed features of monocytic lineage commitment: FAB M4 (n = 3) and FAB M5 (n = 5). However, in group I, patient #5 presented as AML FAB M2.

Successful cytogenetic studies were possible in 6 of the 9 patients. In group I, 3 of 5 patients had balanced translocations involving the 11q23 region. Patient #3 and #4 disclosed a t(9;11)(q21;q23) and patient #5 t(1;11)(p36;q23). Patient #2 had a trisomy of chromosome 8, which is a common finding in AML. In group II, the cytogenetic studies showed del(6)(q) in patient #7 and del(20)(q?) in patient #9.

In group I, patient #5 was a girl with a sAML following an AML. The morphology was M4Eo at diagnosis of ''de novo'' AML and was M2 at diagnosis of sAML. Moreover, cytogenetic studies were clearly different in the primary AML [46 XX/ der(7)/t(7;?)(q32;?)] and in the sAML [t(1;11)(p36;q23)].

In an attempt to achieve a complete remission, all the patients received chemotherapy at the time of the diagnosis of sAML. Seven (#1 to #4 in group I and #7 to #9 in group II) were treated with the regimen previously described (AIE) (27). Patient #6, in group II, only received cytarabine and doxorubicin. Patient #5, in group I, received cytarabine and mitoxantrone because the AIE combination had already been administered to treat her

TABLE II. Treatment and Outcome of sAML

Group I. Prior Hematologic Malignancies	Therapy to Induce Remission	Intensification treatment	Response	Outcome
1	AIE	—	Induction death	Death
2	AIE	—	Induction death	Death
3	AIE	HD Ara-C + etoposide	Complete Remission	Alive in complete remission 51+ months
4	AIE	—	Complete Remission	Relapse and died
5	Ara-C/mitoxantrone	BMT	Complete Remission	Alive in complete remission 15+ months
Group II. Prior Solid Malignancies				
6	Ara-C doxorubicin	—	Complete Remission	Alive in complete remission 99+ months
7	AIE	—	Complete Remission	Death in complete remission
8	AIE	—	Induction death	Death
9	AIE	BMT	Complete Remission	Relapse and died

AIE: cytarabine, idarubicin, etoposide; HDAra-C: High-dose cytarabine, BMT: Bone marrow transplantation.

first AML. Treatment and outcome for the whole group are summarized in Table II.

Three patients died during induction (2 in group I and 1 in group II): patient #1 died during a period of neutropenia and varicella-zoster sepsis, and patients #2 and #8 died as a consequence of complications of hyperleucocytosis and disseminated intravascular coagulation. The other six patients achieved a complete remission (3 in each group). Two of these six patients died one month later: patient #4 (group I) relapsed early and died with progressive disease and patient #7 (group II) died in complete remission of an abdominal complication, probably typhlitis. On the other hand, patients #3 and #6 (1 in each group) received 18 months of chemotherapy, after complete remission was achieved. They have been free of disease for 51+ and 99+ months, respectively, from the date of complete remission, with excellent performance status. Patient #5 and #9 underwent an allogeneic bone marrow transplantation. Patient #5 remains leukemia-free 15+ months, and patient #9 relapsed and died at 13 months after complete remission was achieved.

DISCUSSION

The term ''secondary acute myeloid leukemia'' has been used to encompass several different categories of AML. In this group, AML secondary to another malignancy is highlighted.

The mechanisms of the agents that may be considered to blame in the leukemogenesis and the different groups of sAML according to distinctive features are extensively reported in the literature [16–17].

Analyzing our series, the 3 patients who presented with balanced translocations, involving t(9;11) and t(1;11) and the 11q23 region (patients #3, #4, and #5), had received anthracyclines and cyclophosphamide. However, only 2 of these 3 patients had received etoposide or teniposide: patient #3 following an every-other week schedule for a total of 104 weeks and patient #5 on a schedule of 3 consecutive days during induction therapy for AML and two cycles during intensification for 3 consecutive days. Patient #4 received only anthracyclines. Molecular studies were not performed but if the mechanism is the same in these patients, considering that they have the 11q23 region involved, we could assume the hypothesis that all topoisomerase II inhibitors act in a similar way. The distinctive feature of patient #5 would be the FAB M2 subtype, infrequent in topoisomerase II inhibitor-related sAML [18]. Patients #1, #2, and #6 presented similar characteristics of FAB subtype and previous treatment history to the patients discussed above. Cytogenetic studies were not available for patients #1 and #6; patient #2 had a trisomy of chromosome 8, a non-specific finding associated with ''de novo'' AML. We can only speculate about the mechanisms involved in triggering these events.

Patient #9 received chemotherapy with agents known to produce sAML, including high doses of cyclophosphamide. It is likely that the alkylating agents was to blame because he presented with a previous myelodysplastic phase and his cytogenetic study is compatible with loss of genetic material, although chromosome 5 or 7 are not involved.

Patient #7 received a low dose of dactinomycin and patient #8 developed sAML after receiving only two courses of chemotherapy while he was being treated for

retinoblastoma. Because of the short latent period, it is very difficult to imply a specific leukemogenic agent in these patients.

A surprising finding is that patients #3 and #6 achieved prolonged complete remissions with our standard chemotherapy alone. To our knowledge, this finding is not frequent because of the poor prognosis of this group of patients. Pui et al. reported of experience with 17 patients treated exclusively with chemotherapy and only one is alive. These authors stated that they offered BMT to patients with sAML but their thought is that this special disease requires innovative strategies for cure [19]. Recently, Sandler et al. reported 17 children with sAML. Only 3 of them are alive: 1 after only chemotherapy and 2 after BMT [20].

Only 2 of our patients (#5 and #9) benefited from a bone marrow transplantation. Patient #5 is in complete remission after bone marrow transplantation at 15+ months and patient #9 relapsed and died at 13 months. De Witte et al. reported these experiences with patients with myelodysplastic syndrome and sAML. This report concluded that patients with sAML who underwent BMT in complete remission have a comparable prognosis to those with ''de novo'' AML in first remission with BMT (21).

Secondary acute myeloid leukemia is a subject of increasing concern to the pediatric oncologist. Further studies are warranted in order to establish the mechanisms leading to secondary leukemogenesis.

CONCLUSIONS

We conclude that: 1) AML as a second malignancy remains a relatively rare, but devastating sequela of treatments used in children with cancer. 2) We observed in our sAML cases the cytogenetic abnormalities usually associated with alkylating agents and with topoisomerase II inhibitors. 3) Long-term survival can occasionally be achieved with either standard chemotherapy or with allogeneic bone marrow transplantation.

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